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Review Article

Approaching the Sarcopenic Patient with Nonalcoholic Steatohepatitis-related Cirrhosis

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Abstract

Sarcopenia is a well-known complication of chronic liver disease (CLD), and it is almost always observed in patients with cirrhosis, at least in those with decompensated disease. Since nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), is becoming the leading cause of end-stage liver disease, a new scenario characterized by the frequent coexistence of NAFLD, obesity, and sarcopenia is emerging. Although it is not yet resolved whether the bidirectional relationship between sarcopenia and NAFLD subtends causal determinants, it is clear that the interaction of these two conditions is associated with an increased risk of poor outcomes. Notably, during the course of CLD, deregulation of the liver-muscle-adipose tissue axis has been described. Unfortunately, owing to the lack of properly designed studies, specific therapeutic guidelines for patients with sarcopenia in the context of NAFLD-related CLD have not yet been defined. Strategies aimed to induce the loss of fat mass together with the maintenance of lean body mass seem most appropriate. This can be achieved by properly designed diets integrated with specific nutritional supplementations and accompanied by adequate physical exercise. Future studies aiming to add to the knowledge of the correct assessment and approach to sarcopenia in the context of NAFLD-related CLD are eagerly awaited.

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Abbreviations: BCAA, branched chain amino acid; CI, confidence interval; CLD, chronic liver disease; HCC, hepatocellular carcinoma; HMB, beta-hydroxy-beta-methyl butyrate; IL, interleukin; MAP-kinase, mitogen-activated protein kinase; mTOR1, mammalian target of rapamycin 1; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SMI, skeletal muscle mass index.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH),[1] are becoming principal causes of chronic liver disease (CLD) and cirrhosis in Western countries.[2] They are associated with the increasing prevalence of type 2 diabetes mellitus and obesity. Although frequently being a simple epiphenomenon of dysmetabolism, they behave in some patients as a progressive liver disease evolving toward cirrhosis and hepatocellular carcinoma (HCC).[2]

The European Working Group on Sarcopenia in Older People has defined sarcopenia as the loss of muscle strength and mass and reduced physical performance.[3] However, unlike the geriatric literature,[3] in most studies of patients with CLD, the operational definition of sarcopenia considers only muscle mass. In this study, we use the term sarcopenia mainly to refer to studies in which the definition was based on the reduction of muscle mass. Sarcopenia is a very frequent and overlooked complication of CLD. Recently, it has been recognized as a modifiable determinant of liver disease outcomes, whose recognition and periodic assessment are critical because of its strong association with quality of life, morbidity, and mortality.[4–6]

The prevalence of this condition in cirrhosis is very high, ranging from 30 to 70% depending on the population analyzed.[7] Moreover, it is still not clear to what extent the etiology of liver disease is involved in determining the development and progression of sarcopenia. A study demonstrated that the etiology of liver disease was an independent risk factor for sarcopenia, and alcoholic CLD was associated with a faster decline of muscle mass.[4] However, a more recent study found the prevalence of sarcopenia in cirrhosis (47%) was not related to the etiology of liver disease.[8]

From a physiopathological point of view, the role of sarcopenia in patients with NAFLD and obesity is attracting more and more attention. In this context, the increasing prevalence of metabolic abnormalities in the elderly leads to the frequent coexistence of sarcopenia with NAFLD. However it is not clear whether this association is casual or there is a direct link. There is a growing body of literature examining the bidirectional relationship between sarcopenia and NAFLD in the evolution of CLD.[9–12] Although the clinical relevance

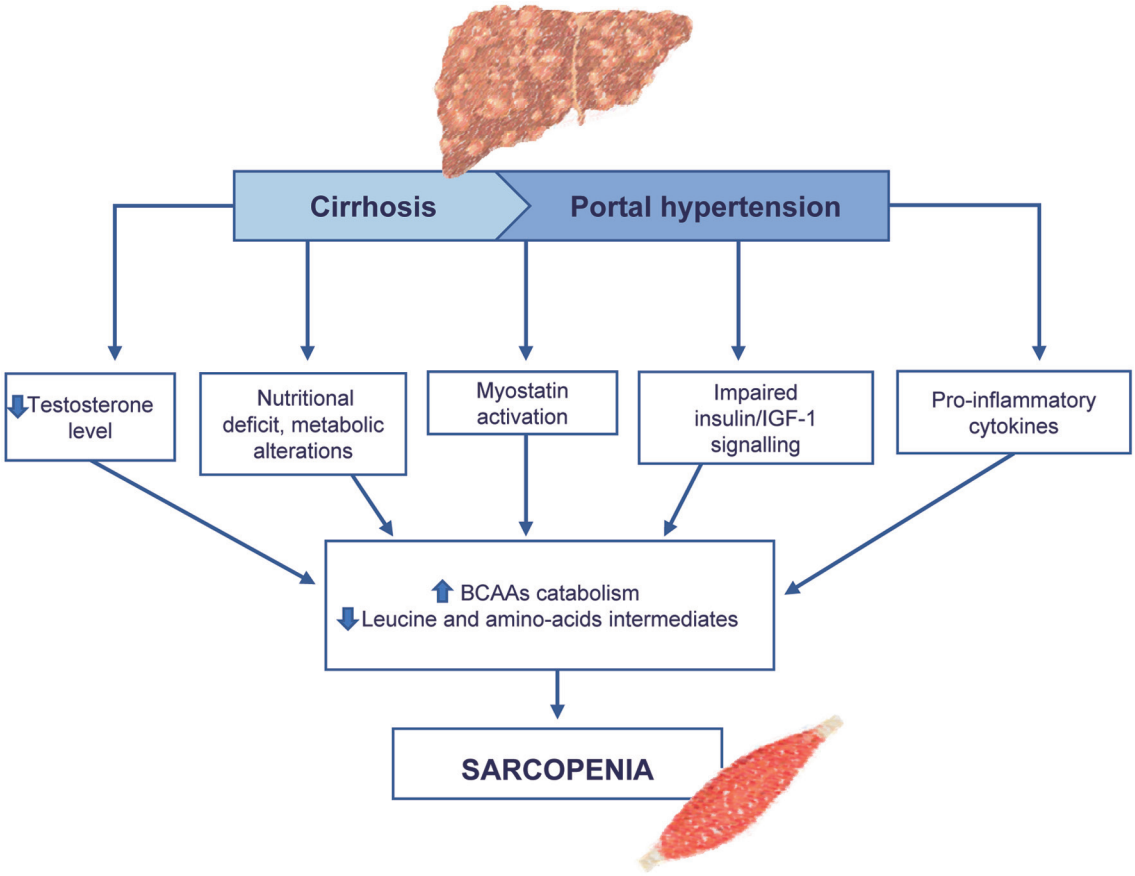

Fig. 1. Summary of the main relevant players contributing to sarcopenia in cirrhosis: hormonal dysregulation, metabolic alterations and pro-inflammatory status. ↑, increase; ↓, decrease; BCAA, branched chain amino acid; IGF-1, insulin-like growth factor-1.

of sarcopenia in the context of CLD is well recognized, with growing evidence on the complex bidirectional pathophysiology of sarcopenia and NAFLD, few reports have focused on the treatment of such patients in that specific setting. The novelty of this review is that in addition to providing an overview of both the physiopathological and clinical aspects of sarcopenia, it aims to focus on the most recent investigations of the management of sarcopenia in this specific setting.

Sarcopenia in CLD

In CLD, the presence of sarcopenia is associated with a reduced quality of life and increased morbidity and mortality.[4,5,13] Moreover, in patients with HCC, the presence of sarcopenia is associated with reduced survival independent of tumor stage and treatment modality.[14] Various techniques have been applied for the diagnosis of sarcopenia in this specific setting; and, to date, the most validated tool is the skeletal muscle mass index (SMI). The SMI is estimated at the third lumbar vertebra (L3-SMI) by computed tomography and magnetic resonance imaging.[15–17] It has the strongest correlation with relative total body skeletal mass.[18,19] Nevertheless, because of radiation exposure and cost, these techniques have not been widely adopted in clinical practice. The use of more accessible and feasible tools, i.e. ultrasound, is still under evaluation.[20,21] In addition, bioimpedance analysis and dual-energy X-ray absorptiometry, although being rapid and safe, have lower diagnostic accuracy in cirrhotic patients because of the interference of ascites and fluid retention. Finally, handgrip strength and physical performance have been associated with adverse clinical outcomes in patients with end-stage liver disease.[22] However, when results are normalized to body mass index, their accuracy is reduced in the context of decompensated liver disease.[23] Moreover, although safe, inexpensive, and reproducible, their reliability may be affected by the presence of covert hepatic encephalopathy and musculoskeletal comorbidities.

The pathogenic mechanisms leading to development of sarcopenia during liver disease are peculiar, as the impairment of liver function and portal hypertension are responsible for unique metabolic disturbances. Indeed, hyperammonemia, glucose level, alteration of protein metabolism [insulin resistance and branched chain amino acid (BCAA) catabolism], hormonal defects (reduced testosterone and increased myostatin levels), inflammation and malabsorption are all important determinants of muscle wasting (Fig. 1).

Sarcopenia and NAFLD

A bidirectional relationship between sarcopenia and NAFLD has been clearly described, and their coexistence has been associated with an increased risk of poor outcomes.[24] However, as most of the available studies are cross-sectional, it is still not clear whether this association is simply the consequence of shared risk factors, results from a causal relationship, or in this case, whether sarcopenia is a conse-

quence or a cause of NAFLD. Sarcopenia increases the risk of NAFLD [odds ratio (OR) 5.16, 95% confidence interval (CI): 1.63–16.33][9] and NASH (OR 2.30, 95% CI: 1.08–4.93) independent of metabolic syndrome features.[10] In addition, it is associated with the stage of liver fibrosis independent of insulin resistance and body mass index (OR 2.05, 95% CI: 1.01–4.16).[10] Small longitudinal studies have even shown a resolution of NAFLD in patients increasing their skeletal mass over time.[25] On the other hand, the presence of NAFLD is associated with a reduction in muscle mass (OR 1.65, 95% CI: 1.19–2.31) and strength (OR 2.29, 95% CI: 1.61–3.26), and with the development of sarcopenia.[26] Intriguingly, recent data also suggest a combined detrimental effect of NAFLD and sarcopenia on the risk of extrahepatic outcomes such as cardiovascular atherosclerotic disease.[27]

Sarcopenic obesity

Overweight and obesity are among the main risk factors for NAFLD. The epidemiological scenario favors the coexistence of sarcopenia and obesity, so called sarcopenic obesity, in patients with CLD.[28–30] In the general population, sarcopenic obesity has been clearly associated with increased risks of morbidity, frailty, and mortality.[31,32] In patients with cirrhosis, the available studies are limited and report prevalence of sarcopenia of between 20% and 35%.[33,34] In the context of liver disease, sarcopenic obesity has been associated with worse outcomes in terms of mortality [hazard ratio (HR) 2.00, 95% CI: 1.44–2.77, $p<0.001$][34] and an increased risk of developing NASH (OR 2.28, 95% CI: 1.21–4.30)[35] and severe liver fibrosis.[12,36] Moreover, in sarcopenic obesity, two major risk factors for the development of HCC, i.e. obesity and NAFLD, cohabit almost constantly in the same subject.[37] Recent data suggest that sarcopenic obese patients undergoing liver resection for HCC have reduced overall survival compared with nonsarcopenic patients (45.6% vs. 61%, $p=0.002$).[38] Notably, sarcopenic obesity is also associated with an increased risk of cardiovascular and metabolic diseases[27,39] and an increased risk of cancer-related mortality compared with sarcopenia without obesity/NAFLD.[40] Overall, in NAFLD patients, sarcopenia should be considered as an adjunctive risk factor for both hepatic and extrahepatic outcomes, although larger studies are expected to clarify its net contribution to the incidence of each event.

Peculiar pathogenesis of sarcopenia in patients with post-NASH cirrhosis and obesity

Sarcopenia occurring in the context of CLD is a multifactorial and complex process, the mechanisms of which have not been fully characterized. Indeed, few preclinical and clinical studies are available, and most of the knowledge has been derived from observational studies.[6] The pathogenesis of sarcopenia in patients with post-NASH cirrhosis is even more peculiar, with a bidirectional interaction between NAFLD and muscle wasting that evolves along all the natural history of CLD. In this context, it is not easy to recognize where deregulation of the muscle-liver-adipose tissue axis begins, and different pathogenic mechanisms have been proposed. Above all, insulin resistance, chronic inflammation, myokine secretion, dysbiosis, and physical inactivity are all considered potential contributors to disease development/progression and to the occurrence of poor outcomes (Fig. 2).[41]

Insulin resistance

In addition to being a characterizing feature of NAFLD, increased insulin resistance is specifically associated with the evolution of CLD toward cirrhosis. The anabolic role of insulin in muscle tissue is well known. In addition to its role in postprandial muscle uptake of glucose through the transmembrane translocation of glucose transporter 4,[42] insulin has an anabolic role in muscular tissue [enhancing protein synthesis[42] and inhibiting proteolysis through the mTOR complex (mTORC) 1 and the MAP-kinase MEK/ERK pathways]. Therefore, insulin resistance is associated with disruption of muscle metabolism,[43] reduced physiological protein turnover rate, downregulation of mitochondrial protein synthesis, increased proteolysis, and an impaired response to oxidative stress.[42,44,45] Insulin resistance also favors hepatic gluconeogenesis through muscle proteolysis, thus contributing to the loss of muscle mass.[24,46] Furthermore, it hinders insulin/mTORC 2 signaling, thereby promoting enhanced production of pro-inflammatory cytokines in adipose tissue.[47] This in turn contributes to a pro-inflammatory state and the acceleration of protein breakdown, increasing the BCAAs catabolism and inducing myostatin expression.[48]

Chronic inflammation

Obesity is characterized by increased secretion of proinflammatory cytokines by visceral fat tissue, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β),[49] which promotes oxidative stress in both muscle and the liver. In the first case, IL6 inhibits the anabolic role of insulin-like growth factor, leading to a reduced myogenesis and increased protein catabolism with muscle mass loss and sarcopenia.[50] Instead, in the context of NAFLD, cytokines have a crucial role in the development and perpetuation of NASH.[51]

Myokines

As skeletal muscle protects against sarcopenia by secreting myokines, their role in liver disease is being increasingly studied. Mainly, the roles of myostatin and irisin have been explored (Fig. 3). Myostatin, the only known negative regulator of muscle growth, has a key role in muscle cell proliferation and differentiation, muscle fiber type transformation, and muscle protein synthesis and degradation.[52,53] Elevated myostatin levels negatively regulate the proliferation and differentiation of satellite cells.[54] The role of myostatin in regulating fat mass has also been explored, yielding clear evidence of its effects on adipogenesis[53] and that its inhibition contributes to fat loss.[55] Myostatin is increased in both obesity[56] and cirrhosis, where deterioration of liver function and hyperammonemia determine a significant elevation of its levels, favoring the development and progression of sarcopenia.[57] Indeed, myostatin levels are an independent predictor of worse survival in patients with cirrhosis.[58]

Irisin is a more recently identified myokine whose role in the evolution of sarcopenia remains unclear, but it is definitively involved. This myokine regulates glucose metabolism and insulin sensitivity in skeletal muscle and may be a biomarker of sarcopenia.[59] Decreased irisin concentrations have been observed in patients with cirrhosis,[60] and were found to be independently associated with the presence of sarcopenia (OR 0.993, $p<0.001$). Increasing irisin may be an important target in the treatment of sarcopenia; notably, physical activity is capable of achieving this goal.[61] Some reports have challenged the association of irisin levels with sarcopenia in cirrhosis,[62] and it is still not known whether the lower irisin concentrations observed in CLD are caused by muscle wasting or vice versa.

Myokines have demonstrated a possible role throughout the entire natural history of NAFLD. For example, irisin has a protective role by averting hepatic steatosis, improving

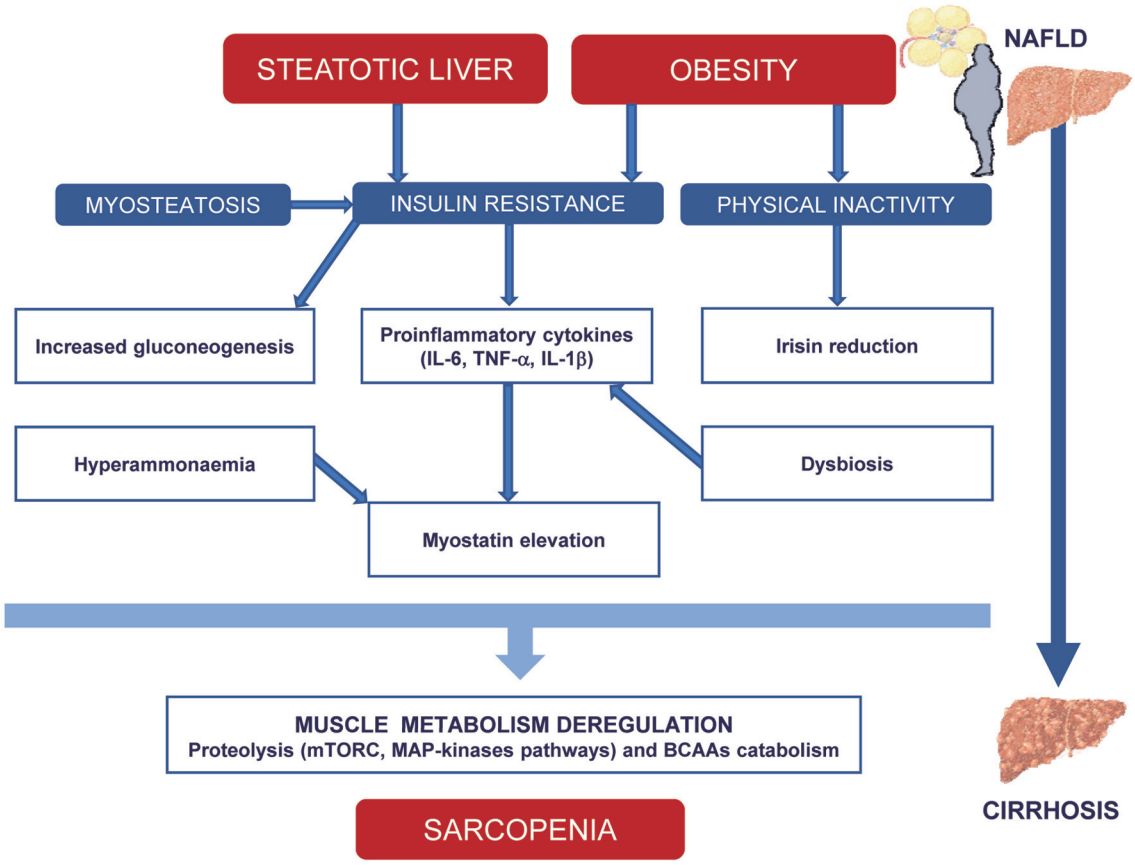

Fig. 2. Liver-muscle-adipose tissue axis deregulation as the trigger of sarcopenia during the natural history of NAFLD. Insulin resistance is a key determinant of proteolysis and BCAAs catabolism; obesity, through the associated pro-inflammatory status, and physical inactivity contribute to disturbance of muscle metabolism. When liver disease progresses to advanced fibrosis/cirrhosis, hyperammonemia contributes to myostatin axis deregulation and muscle catabolism. Dysbiosis and endotoxemia foster chronic inflammation, oxidative stress, and insulin resistance. BCAA, branched chain amino acid; IL-1β, interleukin-1 beta; IL-6, interleukin-6; NAFLD, nonalcoholic fatty liver disease; MAP-kinase, mitogen-activated protein kinase; mTORC, mammalian target of rapamycin complex; TNF-α, tumor necrosis factor-alpha.

insulin resistance, and inducing the production of fibroblast growth factor 21.[24] Conversely, myostatin contributes to hepatic fibrogenesis. In addition, a recent study performed in patients with NAFLD showed an association between fibrosis stage, sarcopenia, and irisin concentration.[63]

Dysbiosis

Several studies have found a significant correlation between dysbiosis and obesity, as well as between gut microbiome dysregulation and liver cirrhosis.[64,65] The obesity-related gut microbiome was shown to increase intestinal permeability and the secretion of lipopolysaccharide.[65] Similarly, the gut dysregulation observed in cirrhosis is characterized by increased intestinal permeability and endotoxemia[66,67] that contribute to chronic inflammation, oxidative stress, and insulin resistance during sarcopenia development and progression.

Physical inactivity

Physical activity is reduced in cirrhotic patients and this could depend on liver related factors, e.g., reduced ventilatory capacity, decreased inspiratory pressure, etc., or unrelated factors, e.g., oxygen reduction caused by anemia and/or blood flow alterations.[68,69] In addition, older age and other comorbidities can further contribute to physical inactivity. Finally, a sedentary lifestyle and physical inactivity are often associated with NAFLD, contributing to the development of overweight and obesity. All these factors, frequently coexisting in patients with fibrotic CLD and post-NASH cirrhosis, make physical inactivity an important contributor to the progression of sarcopenia in this clinical context.[70–73]

Myosteatosis

Recently, fat infiltration of muscle, called myosteatosis, has been associated with increased mortality and morbidity, especially in the elderly.[74] In advanced CLD, myosteatosis is prognostic of adverse perioperative outcomes and mortality.[34,75] Notably, the higher the degree of myosteatosis the lower muscle function and mass.[76] A linear relationship between myosteatosis and NAFLD severity has been clearly described.[77,78] In preclinical studies, myosteatosis has been associated with NASH and fibrosis independent of insulin resistance.[79] Myosteatosis shares several pathophysiological mechanisms with CLD, especially in NAFLD, where it reflects inflammation[80] and is directly correlated with both muscular and hepatic insulin resistance,[81] possibly owing to enhanced adipose tissue lipolysis.[82]

Management

Specific strategies to treat sarcopenia in cirrhotic patients have not yet been developed, and the correct approach to sarcopenic obesity and post-NASH cirrhosis is even less

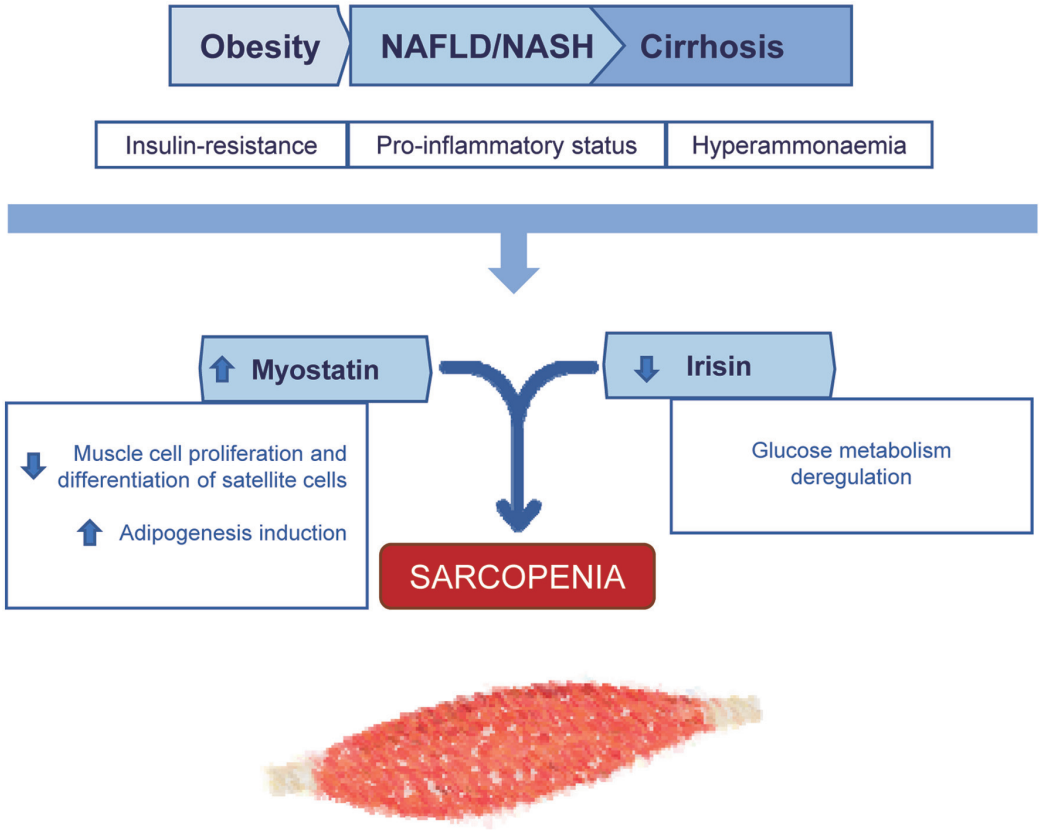

Fig. 3. Myokines and sarcopenia in CLD: A summary of the principal derangements in myokine axis observed in patients with NAFLD. Throughout the natural history of NAFLD-related CLD, insulin resistance, inflammation and finally hyperammonemia increase myostatin and reduce irisin levels. Myostatin negatively regulates proliferation and differentiation of satellite cells, favoring muscle loss and adipogenesis. Concurrently, reduced irisin levels contribute to sarcopenia development and to alterations in glucose metabolism. ↑, increase; ↓, decrease; CLD, chronic liver disease; NAFLD, nonalcoholic fatty liver disease.

clearly defined. In the latter patients, a tailored weight loss should be achieved by reducing fat mass while maintaining lean body mass. To date, there are only a few controlled clinical trials[83–85] in patients with sarcopenic obesity, showing that resistance training leads to an improvement in muscle strength and physical function. Unfortunately, there are no studies specifically carried out in the cirrhotic population. However, several clinical studies, even if rarely performed in the specific context of cirrhosis, support nutritional intervention and physical exercise as the mainstays of current available strategies (see the Supplementary Table 1). Actually, independent from any specific approach to sarcopenia, adequate management of underlying liver disease, its other complications, and all comorbidities, is mandatory (Fig. 4).

Physical exercise

Several recent studies have focused on the benefits of physical exercise in patients with liver cirrhosis.[86,87] Although most of them were carried out in small samples and in the context of compensated cirrhosis, they are consistent in demonstrating that physical exercise has a positive impact on the reversal of sarcopenia, with improvements of muscle mass, strength, and quality of life.[88,89] The European Association for the Study of the Liver practice guidelines for NAFLD recommend for patients with cirrhosis moderate intensity exercise for at least 150 m/week[90] with supervision by expert personnel. Indeed, inappropriate exercise may lead to acute hepatic decompensation with the onset of encephalopathy, ascites, hypoglycemia, worsening portal hypertension, and gastrointestinal bleeding.[91] These recommendations are consistent with those for non-cirrhotic sarcopenic subjects with obesity, i.e. 1 h of exercise three times a week, with 30 m of low-impact aerobic exercise and 30 m of high intensity progressive resistance training.[92] Notably, prolonged physical exercise without adequate nutrient supply can increase muscle catabolism and reduce muscle mass. Therefore, the combination of exercise and dietary intervention guarantees a better efficacy than exercise alone.[93] As sarcopenia in cirrhotic subjects is characterized by both muscle loss and impaired contractile function, a combination of resistance and endurance exercise would probably be the most beneficial.[6] Indeed, endurance or aerobic exercise improve skeletal muscle functional capacity but not necessarily muscle mass.[94] On the other hand, resistance exercise promotes an increase in skeletal muscle mass but it also increases muscle ammonia production and portal pressure.[95] Therefore, a careful preliminary assessment should be aimed at identifying those patients with gastroesophageal varices or an increased risk of hepatic encephalopathy in order to establish a tailored approach.

Nutritional intervention and supplements

Dietary counseling should be a priority in patients with cirrhosis, independent of the etiology. Patients with post-NASH cirrhosis represent a specific challenge. Indeed, they need to lose weight but when trying to achieve this goal through unbalanced and unguided diets, they are at risk of malnutri-

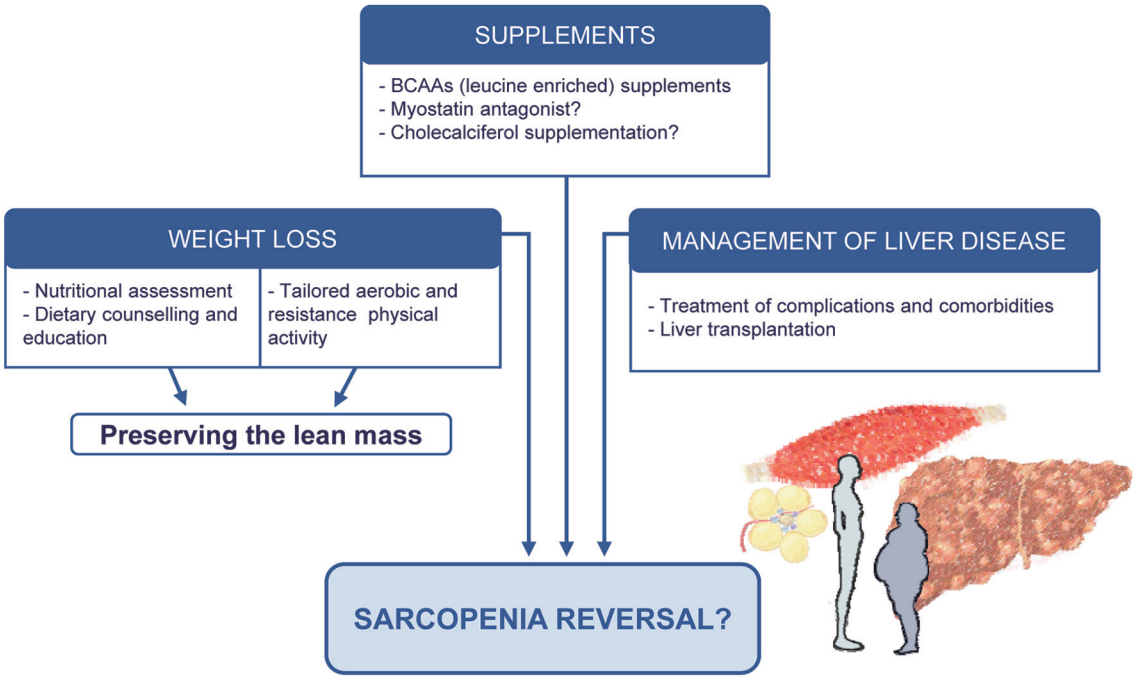

Fig. 4. Treatment of sarcopenia in the cirrhotic patient: a multicentered approach, including weight loss but guaranteeing lean mass preservation, optimal management of liver disease, and specific nutrient oral supplementations**.** BCAA, branched chain amino acid.

tion. Thus, the aim in these subjects is to achieve weight loss while preserving and even increasing lean mass, thus avoiding the risk of further progression of sarcopenia. This can be achieved by paying attention to the evolution of body composition over time and by assessing muscle strength and physical performance with adequate tools.[96] In general, to decrease the loss of muscle mass, a combination of energy restriction and exercise should be preferred with respect to diet alone, with a benefit at least on physical performance.[97] A recent clinical trial showed that a 6-month intervention with guided dietary intake increased muscle mass and strength and improved neurologic symptoms in patients with decompensated cirrhosis and baseline minimal hepatic encephalopathy.[98,99] Furthermore, the available meta-analyses have not been able to demonstrate an impact of specific nutritional supplementations on the risk of mortality,[100] probably because of the very short follow-up in the reference studies.

Macronutrients

In clinical practice, because of the impaired glucose metabolism typical of cirrhosis and the consequent risk of fat and protein catabolism, frequent small meals with a late-night snack containing carbohydrates or proteins is a key nutritional strategy.[101] Notably, essential amino acids have a higher anabolic potential and BCAAs regulate protein metabolism through mTOR signaling.[102] A recent meta-analysis confirmed that, in the context of cirrhosis, late evening snacks containing BCAAs are capable of reversing anabolic resistance and sarcopenia.[103] Several studies have demonstrated that BCAAs improve quality of life and reduce the incidence of hepatic encephalopathy,[104] but the largest meta-analysis of studies in patients with hepatic encephalopathy did not find an impact on mortality.[105] Conversely, long-term supplementation of cirrhotic patients with BCAAs has been clearly associated with a reduced risk of decompensation and an improved nutritional status[106] but in the absence of specific data on the effect on muscle function and mass. Leucine is a BCAA shown to have a positive clinical impact through its active metabolite beta-hydroxy-beta-methyl butyrate (HMB)[107] and its anticatabolic activity in skeletal muscle.[108] Indeed, in cirrhotic patients, 12 weeks of leucine supplementation (10 g/day) combined with physical activity led to improvements of both muscle mass and of quality of life.[109] Moreover, HMB was found to be associated with an improvement of muscle function in a small pilot randomized controlled trial.[110] Avoiding added sugars is recommended. Indeed, they have been associated with derangement of the insulin axis and reported to contribute to the development of NAFLD and sarcopenia mainly through the induction of inflammatory signaling and consequent fat infiltration.[111] In addition, the possible role of eicosapentaenoic acid and docosahexaenoic acid supplementation has not been definitively clarified.[112] Indeed, although polyunsaturated fatty acids are expected to have a beneficial effect on both NAFLD and sarcopenia,[113] the available studies do not indicate that their supplementation provides benefit to sarcopenic patients.[114]

Other supplements

Although the role of cholecalciferol in skeletal muscle metabolism is well-recognized and low vitamin D levels are associated with sarcopenia, placebo-controlled randomized clinical trials aimed to evaluate the effect of oral vitamin D supplementation for preventing or treating sarcopenia have generated conflicting results.[115] As vitamin D deficiency has been associated with the development and progression of NAFLD,[116,117] its possible role in sarcopenic patients with post-NASH cirrhosis is even more interesting. Furthermore, even though the association of cholecalciferol deficiency with CLD and mortality has been clearly described,[118] there is insufficient evidence to support the role of vitamin D supplementation for the treatment of sarcopenia even in the specific context of cirrhosis. Lastly, the possible role of myostatin

antagonists, such as follistatin,[119] in patients with cirrhosis is of particular interest; however, no clinical evidence has been acquired so far.

Strengths and limitations

This review provides some insights into the pathophysiology and treatment of sarcopenia in NAFLD-related CLD, with direct reference to the most relevant recent literature. Currently, a body of evidence supports the potential benefit of nutritional supplements (i.e. BCAAs and HMB)[83,98,102–104,106,110,115] as well as physical exercise[84–88,97,108] because of their multimodal mechanisms of action that target most metabolic imbalances present in these patients. However, the reliability of the data is partially reduced by the limited number of relevant studies, their small sample sizes, and the heterogeneity of the patient populations included. Indeed, analysis of patient cohorts with different CLD etiologies and stages is the main limitation when aiming to reach a conclusion of the impact of sarcopenia and different approaches implemented to inhibit it using hard clinical outcomes (CLD decompensation, death).[105] In this direction, large randomized controlled trials with well-defined diagnostic criteria, diagnostic tools, interventions, endpoints, and follow-up duration are required. Despite the current limitations, here we have reported the available evidence supporting the benefits of both pharmacological and nonpharmacological interventions for the treatment of sarcopenia in NAFLD-related CLD. Moreover, we have highlighted the need to improve clinician awareness of the pathophysiological relevance of sarcopenia in this context, because, as always, recognizing a problem is the first step in tackling it.

Conclusions

The high prevalence of sarcopenia in CLD of any etiology and its significant prognostic role warrant efforts to improve early recognition and intervention. In the context of post-NASH cirrhosis, sarcopenia is the meeting point of two different pathophysiological determinants, the dysmetabolic and catabolic ones, which interact in a vicious cycle. To date, there is very limited evidence concerning the optimal strategies to assess and treat sarcopenia in cirrhotic patients. Studies with larger sample sizes, adequate follow-up, and hard clinical outcomes as primary endpoints are eagerly awaited to identify the nutritional, pharmacological, and nonpharmacological interventions capable of reversing sarcopenia during CLD.

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None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (PG, VF), acquisition of data (VF, AF, GDP), analysis and interpretation of the data and drafting of the manuscript (VF, AF, GDP, GD), critical revision of the manuscript for important intellectual content (PG, FT), and study supervision (UVG, AP). All authors made significant contributions to this study and have approved the final manuscript.

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